MEDIASTINAL LEUKOSARCOMATOSIS (STERNBERG).

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The term "leukosarcomatosis," which was introduced by Carl Sternberg, about 1905, ought to include all tumor-like (that is to say, sarcoma-like) leukemic growths (whether the cells of the growth belong to the lymphoid or to the myeloid series) associated with or followed by leukemic changes in the circulating blood. The cases collected by Sternberg presented the features of acute or subacute leukemia associated with tumor-like formations in various positions. He regarded cases of chloroma or chlorosarcomatosis as constituting one striking type of his "leukosarcomatosis," and at the end of his paper on chloroma, published in 1905,[1] he proposed the term leukosarcomatosis (Leukosarkomatose) for the cases which were formerly regarded as a combination of leukemia and lymphosarcomatosis, and which he had elsewhere separated off as a distinct group. Cases of leukosarcomatosis other than chloroma may, in fact, be looked on as cases of chlorosarcomatosis, but without the greenish pigment from which chloroma derives its name. Among the most remarkable cases of the kind are those of "mediastinal leukosarcomatosis" in young persons, in which there is a leukemic blood picture and in which the mediastinal tumor appears to be growing from the remains of the thymus gland. In the following case and in some others, to which we shall refer later, the growth was moulded over the parietal pericardium, covering it like a blanket.

The case was that of a young man, F. K., aged eighteen years, a clerk, who was admitted to the German Hospital on March 21, 1914. The patient while in the hospital was under the care of Dr. K. Rupp, to whom our thanks are due for permission to publish this report. On admission he was fairly well nourished, and said that he had been ailing for one month and had suffered from pains in the right side. His superficial lymphatic glands on both sides of the neck, in both axillæ, and in both groins were moderately enlarged, and so were his tonsils. His spleen, which felt hard, extended downward to just below the umbilical level, and the liver was likewise somewhat enlarged. There was slight pyrexia of an irregular type. The urine was free from albumin. There was a moderate pleural effusion on the right side, and 800 c.c. of this fluid were aspirated on March 25; its specific gravity was 1008; clear; slightly red from admixture of blood.[2] A blood count on March 23 proved the case to be one of leukemia; the white cells were estimated at 131,000 to the cubic millimeter of blood. Treatment by the application of roentgen rays and the internal use of arsenic was commenced soon after the patient's admission, but the roentgen-ray therapy was discontinued after the first séance, and the case ran the invariably fatal course of acute or subacute leukemia.[3]

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[1] Carl Sternberg, Zur Kenntnis des Chloroms (Chloromyelosarkom), Beiträge zur path. Anat. und zur allg. Path., Jena, 1905, xxxvii, 437–454.

A blood examination made on March 31 gave: red cells 3,000,000 and white cells 167,500 to the cubic millimeter of blood; hemoglobin, 49 per cent. Of the white cells, 96 per cent. were lymphocytes (mostly rather large), 2 per cent. were polymorphonuclear neutrophiles, and 2 per cent. were transitionals. A few nucleated red cells were seen. The erythrocytes showed no poikilocytosis, anisocytosis, or polychromatophilia. On April 12 the right pleural effusion was again tapped and 1700 c.c. of a cloudy fluid was removed; it was of specific gravity 1015, and yielded a slightly sanguineous coagulum on standing.

In the second half of April it was obvious that the patient was going down hill and rapidly losing strength. There had been much epistaxis. There were purpuric spots (petechiæ) on the legs and retinal hemorrhages in both eyes. Since admission there had often been slight pyrexia (up to 100° F.). The lower extremities became edematous and the petechiæ gradually increased in number; dark ecchymoses appeared spontaneously about both eyes. On April 23 a fresh blood count gave 1,500,000 red cells and 176,000 white cells to the cubic millimeter of blood; nearly all the white cells were large lymphocytes, and no nucleated red cells were seen on that occasion. About that time the feces were fluid and colored red with blood. The spleen diminished somewhat in size toward the end of life, and a swelling appeared on the right side of the upper jaw (of septic dental origin?). The patient died on May 5, 1914, six and a half weeks after admission.

In regard to the nature of the mononuclear white cells (large lymphocyte type) in the present case, Dr. Gordon Ward kindly examined some blood films (of April 27) for us. He thought they were precursors of the ordinary lymphocyte type and that the leukemia was of the lymphemic type. He pointed out that there were many "Rieder cells"[4] present, but that he saw no nucleated red cells and no myelocytes such as one would expect to be present in any myeloid leukemia, even in an acute myelemia.

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[2] In cases of leukemia, pleural effusions are seldom noted during life; they are said to be always colored from admixture of blood. At the Société médicale des hôpitaux de Paris (Bull. et Mém., 1914, 3d series, xxxvii, 545), in March, 1914, Gouget and Mdlle. de Pfeffel described a case of leukemia "à forme pleurétique" in a woman, aged sixty-three years. Her illness commenced suddenly with signs of pleurisy on the right side, and she died ten days later. Her blood contained 1,302,000 red cells and 62,000 white cells to the cubic millimeter, and 68 per cent. of the white cells belonged to the "large non-granular mononuclear" class. The pleura was found sprinkled with little granules made up of the white cells.

[3] Neither roentgen-ray therapy nor arsenic nor any known form of treatment appears to be of any use in cases of acute (and subacute) leukemia.

NECROPSY. On examining the contents of the thorax a hard white tumor-like mass was seen in the superior mediastinum, apparently originating at the site of, and enclosing the remains of, the thymus gland. It spread downward over the parietal pericardium, almost the whole of which it enclosed, "like a blanket." There was some pleural effusion on the right side. The heart (weight 11 ounces), lungs, and aorta showed nothing special. The spleen was enlarged, weighing 27½ ounces and measuring 18 x 12 x 6 cm. It was of rather hard consistence and contained several anemic infarcts (doubtless of leukemic thrombotic origin), and its substance, excepting the infarcts, was of a dark crimson color. There were several perisplenitic adhesions. The liver was enlarged, weighing 80 ounces, but on section by naked-eye examination it appeared normal. The kidneys, weighing together 13 ounces, were pale. Nothing special was noted in the pancreas, alimentary canal, or thyroid gland. The brain and spinal cord were not examined. The lymphatic glands were moderately enlarged throughout; many of them were white, others were of a reddish color; among the latter were some of the mesenteric and some of the cervical glands. The right humerus was sawed open longitudinally and the marrow in the shaft was found to be of a bright red color.

MICROSCOPIC EXAMINATION. 1. *The Tumor-like Mass in the Mediastinum Enclosing the Remains of the Thymus Gland.* What remained of the thymus gland consisted of lymphoid cells with a follicular arrangement, and included a few calcified bodies, probably derived from Hassall's corpuscles. The tissue outside the capsule of the thymus gland was permeated with, and in fact consisted of, lymphoid cells of the "large lymphocyte" class, *i. e.*, of the same type as those within the capsule.

2. *A Portion of the Tumor-like Mass Outside the Remnant of the Thymus Gland.* It was found to consist chiefly of the same kind of lymphoid cells of the "large lymphocyte" class as those seen in No. 1. The tissue included scattered fat vesicles, and was evidently connective tissue densely permeated by the lymphoid cells in question.

3. *Part of the Growth from the Parietal Pericardium.* It consisted of fatty connective tissue permeated with the same kind of lymphoid cells.

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[4] "Rieder cells" or "Rieder lymphocytes" are cells of the large lymphocyte class, but with kidney-shaped or multilobed nucleus, their cytoplasm resembling that of the lymphocytes in regard to staining affinities.

4. *A Lymphatic Gland from the Left Side of the Neck.* The gland showed hyperplasia of lymphoid cells, and the surrounding connective tissue (outside the capsule of the gland) was infiltrated with the same kind of lymphoid cells.

5. *The Spleen.* Sections showed relative increase in the size of the lymph follicles (Malpighian corpuscles) and congestion of the splenic pulp between the lymph follicles. But the whole splenic substance was more or less permeated with lymphoid cells (of the same kind as those seen in the microscopic examination of the other organs). A few eosinophile cells were seen in the sections. The Prussian-blue reaction for free iron gave a negative result.

6. *The Liver.* A section of the right lobe showed great interacinous infiltration with the same kind of lymphoid cells. A section of the liver was examined for the Prussian-blue reaction (for free iron), with negative result.

7. *Kidney.* The sections showed patchy infiltration of the organ with lymphoid cells of the same type. The cells in question separated the tubules and glomeruli of the kidney without destroying them. The renal tubules appeared to have undergone extreme "cloudy swelling." The Prussian-blue reaction for free iron gave a negative result.

8. *Bone-marrow from the Shaft of the Right Humerus.* It consisted chiefly of lymphoid cells, similar to those permeating the other organs. Some of these lymphoid cells were undergoing division. There were likewise erythroblasts, and, scattered here and there, were bone-marrow giant-cells, eosinophile cells, and scanty fat vesicles.

Summing up it may be said that all the tissues examined were permeated with a kind of lymphoid cell, the mediastinal "tumor" being perhaps merely a local exaggeration of this lymphoid permeation, connected with, and apparently growing from, the remnant of the thymus gland. The conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which during the patient's life constituted by far the greatest portion of the white cells in his circulating blood. As has already been stated, these cells should probably be regarded as cells of the large lymphocyte class, or rather as "lymphoblasts," the precursors of lymphocytes, rather than as "myeloblasts," the non-granular precursors of the myelocyte series. Here it may be mentioned that the guaiac reaction with the patient's blood (tried according to the directions given in Otto Naegeli's[5] work) gave a negative result. Dr. J. S. Dunn[6] was kind enough to try the oxydase reaction for us in blood films taken during life and sections of the tissues made after the patient's death. He found that the vast majority of the mononuclear (lymphoid) cells gave no oxydase reaction, but that a few did give one, the proportion of positively reacting cells being more considerable in the kidney than in the other organs.

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[5] Blutkrankheiten und Blutdiagnostik, second German edition, Leipzig, 1912, p. 93.

[6] The Use of the Oxydase Reaction in the Differentiation of Acute Leukemias, Quarterly Journal of Medicine, Oxford, 1913, vi, 293.

Sections of the various organs stained by the Unna-Pappenheim methyl-green-pyronin method showed that the cells under discussion (of which the cell-infiltrates practically consisted) sometimes tended, according to their staining reactions, to resemble plasma cells, some of them staining almost like plasma cells, though most of them stained like "large lymphocytes." (We have to thank Dr. J. C. G. Ledingham for looking through the specially stained sections for us.)

OTHER CASES. With our present case may be compared a case of mediastinal leukosarcomatosis described by W. Mager[7] (of Brünn) in 1909. His patient was a man, aged twenty-one years, with a pleural effusion (a transudate) and enlargement of the lymphatic glands in the neck and axilla on the side of the effusion. Dilated thoracic veins, subconjunctival ecchymoses, enlargement of the spleen, and dyspnea, were notable features of the clinical picture. A blood count gave 810,000 white cells to the cubic millimeter of blood, of which 95 per cent. were large mononuclear cells of the kind found in C. Sternberg's leukosarcoma cases. The necropsy showed the presence of a large infiltrating tumor-like mass in the anterior mediastinum, consisting of characteristic cells of the same class. The illustration accompanying Mager's paper shows that the condition was very similar to that found in the case which forms the chief subject of our present communication. The main mass of the tumor was in the region of the thymus gland, but prolongations downward had grown over the parietal pericardium, enveloping it like a blanket.

Another remarkable case of mediastinal leukosarcomatosis was reported by W. D. O'Kelly[8] in 1914. The patient was a tall, slender youth, aged nineteen years. He got a severe wetting on August 13, 1913, and felt unwell after it. He then seemed weak and "remained idle." He was admitted to the hospital on September 19, 1913. The temperature was 100° F. The splenic dulness was somewhat increased. There was stomatitis. The blood serum, which had a milky appearance, gave a negative Wassermann reaction for syphilis.

Blood Examination. There were 1,472,000 red cells and 295,000 white cells to the cubic millimeter of blood; hemoglobin, 26.25 per cent. The differential count of white cells gave: polymorphonuclear neutrophiles, 1.5 per cent.; neutrophile myelocytes, 0.5 per cent.; lymphocytes, 15.5 per cent.; large mononuclears,

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[7] Zur Klinik der Leukosarkomatose, Wiener med. Wchnschr., 1909, lix, column 1877.

[8] Dublin Journal Med. Sci., 1914, cxxxvii, 409.

3.5 per cent.; myeloblasts and lymphoblasts, 79 per cent. The general condition of the patient became steadily worse, though the stomatitis disappeared. His temperature ranged between 100° and 104° F. His pulse was 100 to 140 per minute and his respiration was 24 to 36. There was slight epistaxis on October 3. Death took place on October 5, 1913. Clinically, the author pointed out, the case was one of acute leukemia of the "large lymphocyte" class, and the "leukosarcomatosis" was not discovered during life. At the postmortem examination, "on removing the sternum a large pale pink mass, the size of a closed fist, was seen filling up the superior mediastinum. It was moulded on the pericardium and the great vessels were surrounded by it. The trachea was embedded in its posterior wall. On section it was firm, with a few necrotic areas of the size of a six-penny piece. None of the usual thymic remnants were seen. . . . No pleural adhesions were present." No evidences of tuberculosis were discovered. A specimen of the blood from the heart taken at the time of the necropsy yielded a pure culture of B. coli. Microscopic examination showed the mediastinal mass to have the structure of Sternberg's leukosarcomatosis. It apparently contained no concentric corpuscles of Hassall. There was typical cellular (leukemic) infiltration of the kidneys and liver. For further details the reader must be referred to the original paper.

Another excellent illustration of mediastinal leukosarcomatosis is furnished by a specimen in the Pathological Museum of St. Bartholomew's Hospital, London, classified as "sarcoma with lymphemia" among "Diseases of the Thymus and Thyroid Glands."[9] The patient, a girl, aged five years, who died after five weeks' illness, had a blood picture of lymphocytic leukemia. The red cells were estimated at 2,000,000 per cubic millimeter of blood; the white cells numbered 60,000 per cubic millimeter, of which 88.5 per cent. were lymphocytes. At the necropsy the anterior mediastinum was found to be occupied by a large solid yellow growth, which lay upon the upper half of the pericardium and partially enveloped the lower two-thirds of the trachea. The parietal pericardium, but not the visceral pericardium, was infiltrated. The kidneys of the patient were infiltrated with yellowish secondary deposits, consisting of small round cells.

Remarks. The above-described cases were all characterized by the presence of acute or subacute leukemia in association with a tumor-like mass in the superior mediastinum, which had spread downward over the pericardium. The following case is somewhat different. The patient, S. S., was a well-developed man, aged fifty-seven years, admitted to the hospital under one of us (F. P. W.) on May 27, 1915, with a history of having been ill for about five months. In the hospital there were general bronchitic signs, with impaired resonance at the base of the right lung; there was at one time some purulent sputum containing blood. The breathing was slightly stridulous, and there seemed to be inspiratory difficulty. There was never any fever in the hospital, but rapidly-increasing weakness was obvious. The patient died on June 9, 1915. The postmortem examination showed the presence of a large, hard, white, tumor-like mass in the mediastinum. It included, and seemed to be growing from, the pigmented bronchial glands at about the level of the bifurcation of the trachea. It enclosed the descending portion of the thoracic aorta, the lower portion of the trachea, and both bronchi, causing bronchial stenosis, the lumen of each bronchus being diminished by about half of its diameter. The growth in question infiltrated the lower part of the right lung, and a small portion of the left lung close to the left bronchus. The other organs showed no special macroscopic change, and there was no noteworthy enlargement of lymphatic glands other than the mediastinal ones. The microscopic section (for which we are greatly indebted to Dr. Hans Schmidt) showed that the mediastinal growth consisted practically entirely of round cells of the lymphocyte of lymphoblast type. Below the capsule of the kidney and in the portal spaces of the liver were small infiltrates of the same kind of round cells. It is unfortunate that no examination of the patient's blood was made, but there can hardly be any doubt that the case belonged to Sternberg's "leukosarcomatosis" group, though it differed somewhat from the preceding cases in regard to the position of the main tumor-like mass.

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[9] St. Bartholomew's Hospital Reports, London, xlii, 207, No. 2309, b. 4.

From the pathological-anatomical point of view there are, of course, besides the mediastinal group and the striking chloromatous group, several other varieties of Sternberg's "leukosarcomatosis." Cases need not necessarily be associated with obvious leukemic changes in the circulating blood, and it is permissible to speak of "aleukemic" cases when such changes are wanting. One of us has recently written on a remarkable form of leukosarcomatosis occurring chiefly in children in which the kidneys are permeated with round cells of the lymphocyte or lymphoblast type, and in which there may or may not be obvious leukemic changes in the circulating blood.[10]

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[10] F. Parkes Weber, A Note on Lymphocytomatosis or Lymphoblastomatosis, especially of the Kidneys, British Journal of Children's Diseases, London, 1915, vol. xii, 268–274.